6 months in the ELS-treated and 0 at both time points in the control patients.

The rate of all SAEs was higher for the ELS-treated than for control patients, with 43% and 16%, respectively, requiring hospitalization, primarily for respiratory SAEs (39% of treatment and 15% of control patients). Two patients in the treatment group died (1 treatment related).

The individual patient data at 6 months showed that the improvement in FEV_1 ranged from a nearly 25% reduction to an approximately 120% increase in the ELS-treated patients. The median change in FEV_1 was approximately 19% and the mean change was approximately 28% in the ELS-treated patients, which is comparable with surgical LVR outcomes, stated Dr. Washko.

Consistent Targeted Dosing of BUD Benefits Asthma Patients Needing Long-term Oral Corticosteroids

Written by Mary Beth Neirengarten

In patients with severe asthma who depend on long-term oral corticosteroid therapy, additional treatment with consistent doses of budesonide (BUD) delivered by a novel inhalation system significantly improved lung function and control of asthma exacerbations.

Sebastian Canisius, MD, Vectura GmbH, Frankfurt, Germany, reported outcomes from the AKITA Inhaled Steroid Suspension for Inhalation in Subjects With Asthma [AICS; NCT01200108; Canisius S et al. *Am J Respir Crit Care* 2014]—a Phase 2/3, randomized, placebo-controlled trial featuring 4 arms and parallel groups. In it, researchers evaluated the efficacy of a novel computer-controlled, compressor-driven inhalation system (Akita; Activaero) that delivered consistent doses of BUD as add-on treatment in patients with severe asthma on long-term oral corticosteroids therapy.

In the study, adult patients (age, 18 to 65 years; Table 1) from 27 respiratory outpatient centers in Germany, Poland, and Ukraine were randomly assigned in a double-blind fashion to 1 of 4 treatment arms for 18 weeks:

1. AICS-BUD (1 mg): AKITA-inhaled corticosteroid+BUD (1 mg, twice a day [BID]; n=80)
2. AICS-BUD (0.5 mg): AKITA-inhaled corticosteroid+BUD (0.5 mg, BID; n=39)
3. AICS-placebo: AKITA-inhaled corticosteroid+placebo (BID; n=40)
4. CN-BUD: open-label treatment with BUD (1 mg, BID) administered with a conventional nebulizer (n=40)

The doses of long-term corticosteroid therapy were tapered until Week 14, and patients were followed to Week 20.

Table 1. Baseline Characteristics[a]

	AICS-BUD				
	1 mg (n=80)	0.5 mg (n=39)	Placebo (n=40)	CN-BUD (n=40)	Total (n=199)
Age, years	52.0 ± 8.8	51.6 ± 10.0	52.3 ± 9.2	49.7 ± 10.6	51.5 ± 9.5
Female	56 (70.0)	14 (64.1)	24 (60.0)	24 (60.0)	129 (64.8)
Duration of asthma, years	19.2 ± 12.1	21.2 ± 12.6	19.9 ± 11.7	18.4 ± 10.6	19.6 ± 11.8
MiniAQLQ, total score	3.6 ± 0.9	3.7 ± 1.0	3.7 ± 0.7	3.6 ± 1.0	2.6 ± 0.9
ACQ, total score	3.2 ± 0.8	3.2 ± 0.9	3.0 ± 0.7	3.1 ± 1.0	3.1 ± 0.80
Predicted FEF_{25-75}, %	59.0 ± 11.8	56.4 ± 9.5	57.0 ± 11.2	58.1 ± 12.3	57.9 ± 11.3
FEV_1, L/s	1.11 ± 0.56	1.00 ± 0.51	1.00 ± 0.51	1.11 ± 0.61	ND
OCS,[b] baseline dose, mg/day	10.0 ± 7.1	10.6 ± 9.0	10.4 ± 8.2	10.1 ± 6.2	10.2 ± 7.5
SABA, puffs/day[c]	4.6 ± 3.7	4.0 ± 3.6	4.3 ± 3.6	4.3 ± 3.1	4.4 ± 3.5
Ex-smokers[d]	7 (8.8)	4 (10.3)	3 (7.5)	9 (22.5)	23 (11.6)
Pack-years	5.3 ± 3.0	5.5 ± 2.6	8.0 ± 1.0	5.2 ± 3.1	5.3 ± 3.0

ACQ=Asthma Control Questionnaire; AICS-BUD= AKITA-inhaled corticosteroid; AQLQ=Asthma Quality of Life Questionnaire; BUD=budesonide; CN=conventional nebulizer; FEF_{25-75}=forced expiratory flow from 25% to 75% of vital capacity; FEV_1=forced expiratory volume in 1 second; ICS=inhaled corticosteroid; ND=not determined; OCS=oral corticosteroids; SABA=short-acting beta agonist.

[a]Values in mean ± SD or n (%).

[b]All patients were receiving OCS; prednisone was specified by the protocol for use during the study.

[c]n=75, 34, 37, 38, and 184 for 5 columns in the table.

[d]Study eligibility specified patients were nonsmokers or ex-smokers.

Efficacy was assessed on the basis of lung function parameters, including mean forced expiratory volume in 1 second (FEV_1), as well as mean change in forced expiratory flow from 25% to 75% of vital capacity, which (FEF_{25-75}) that the authors noted is a fairly reliable surrogate marker of small airway function. These lung function parameters were recorded during each patient visit for 2 weeks.

Overall, the study revealed that the dose of long-term oral corticosteroids was reduced in all treatment arms. For patients who received add-on therapy, lung function parameters improved significantly at Week 18 from baseline, whereas no significant improvements were seen in patients in the placebo and conventional nebulizer arms. The mean FEV_1 were 239 mL ($p<0.001$) and 126 mL ($p=0.01$) for AICS-BUD (1 mg) and AICS-BUD (0.5 mg), respectively, and 93 mL ($p=0.36$) and 137 mL ($p=0.18$) for placebo and CN-BUD, respectively. Regarding small airway function, the study revealed that patients treated with AICS-BUD (1 mg) had significant improvement in mean FEF_{25-75} from baseline to Week 18 compared with patients in the AICS-placebo arm. The study also indicated that patients treated with AICS-BUD (1 mg), compared with those treated by CN-BUD, had fewer asthma exacerbations (7.5% vs 22.5%), a longer mean time to first exacerbation (96.5 vs 50.1 days), and a smaller subsample of patients who experienced asthma instability (15.0% vs 25.0%).

These findings show an improvement in lung function 12 weeks after initiation of consistent dosing of BUD via a novel delivery system. Without controlling for differences among treatment groups, there appears to be greater benefit of consistent delivery of BUD (1 mg) over similar dosing with a conventional nebulizer.

CYT003-QbG10 Not Effective in Uncontrolled Allergic Asthma

Written by Emma Hitt Nichols, PhD

Treatment with the A-type CpG oligodeoxynucleotide CYT003-QbG10 did not improve asthma control or lung function in patients with allergic asthma not adequately controlled with inhaled corticosteroids. Thomas Casale, MD, University of South Florida, Tampa, Florida, USA, presented data from the Randomized, Placebo-Controlled, Phase IIb Dose-Finding Study of CYT003-QbG10, a TLR9-Agonist, for Treatment of Uncontrolled Moderate to Severe Allergic Asthma [NCT01673672; Casale T et al. *Am J Respir Care Med* 2014].

CYT003-QbG10 is an A-type CpG oligodeoxynucleotide that activates toll-like receptor 9 to inhibit T-cell mediated airway inflammation. A previous study demonstrated that CYT003-QbG10 maintained or improved symptom control in patients with allergic asthma that was controlled with an inhaled corticosteroid [Beeh KM et al. *J Allergy Clin Immunol* 2013]. The purpose of this trial was to determine if treatment with CYT003-QbG10 would achieve similar results in patients with allergenic asthma that was not controlled by inhaled corticosteroids.

In this Phase 2 trial, 365 adults with moderate to severe allergic asthma were randomly assigned to receive 3 different dose levels of CYT003-QbG10 or placebo for 12 weeks. CYT003-QbG10 was administered by subcutaneous injection weekly for the first 4 weeks, then every other week up to 12 weeks. Patients aged 18 to 65 years were eligible if their asthma (Global Initiative Against Asthma steps 3 and 4) was not controlled with standard therapy. The primary outcome was asthma control after 12 weeks, and secondary outcomes included lung function, asthma symptoms, medication score, exacerbation, and quality of life.

Treatment with any dose of CYT003-QbG10 did not significantly change asthma control from baseline compared with placebo, as determined by the Asthma Control Questionnaire (ACQ) score. In addition, there were no significant changes from baseline in lung function or Mini Asthma Quality of Life Questionnaire scores.

Dr. Casale discussed the potential reasons that CYT003-QbG10 failed in this trial, focusing on the differences in study populations between the initial and current study. He noted that the ACQ score and eosinophil count were lower, and lung function was higher, in the patients in the initial study compared with the present study [Beeh KM et al. *J Allergy Clin Immunol* 2013]. He hypothesized that immune modulators such as CYT003-QbG10 may only benefit certain subpopulations. For example, the initial study demonstrated that CYT003-QbG10 treatment resulted in better outcomes in patients with the Th2-hi phenotype, which encompasses patients with higher eosinophil counts [Beeh KM et al. *J Allergy Clin Immunol* 2013]. Dr. Casale further differentiated the 2 study populations by pointing out that in the initial study, the improvement in ACQ score occurred when the corticosteroid dose was tapered to a lower dose and then discontinued. In the current study, no additional benefit was seen with the addition of CYT003-QbG10 to inhaled corticosteroids. Therefore, he suggested that CYT003-QbG10 may be most effective in patients who are not being treated for their asthma and that those with uncontrolled asthma represent the wrong patient population for this therapy.

In conclusion, Dr. Casale stated that although CYT003-QbG10 is not effective in patients with uncontrolled allergic asthma on inhaled corticosteroids, it may be effective